This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 21

See attached form for additional information.

Interagency Report Control No.:

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

1. CERTIFICATE NUMBER: 57-R-0118
CUSTOMER NUMBER: 16294

FORM APPROVED
OMB NO. 0579-0036

KH

Inhibitex Inc
9005 Westside Pkwy
Alpharetta, GA 30004

Telephone: (678) -746-1100

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Atached Listin (b)(2)High, (b)(7)(F)

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY **(Attach additional sheets if necessary or use APHIS Form 7023A)**

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not ye used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use o pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reas such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters					
8. Rabbits			27	111	138
9. Non-human Primates					
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anestetic, analgesic, and tranquilizing drugs, prior to, during, and following actual rese teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and ap Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary inc brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)

SIGNATURE OF (b)(6),(b)(7)(c)

NAME & TITLE OF C.E.O. OR INSTITUTIONAL OFFICIAL (Type or Print) (b)(6),(b)(7)(c)

DATE SIGNED 11-13-07

APHIS FORM 702 (AUG 91) which is obsolete.)

Column E Explanation

1. **Registration Number: 57-R-0118 / 16294**

2. **Number of animals (in category E) used in this study: 111**

3. **Species (common name) of animals used: Rabbit**

4. **Explain the procedure producing pain and/or distress:**

   The studies described here are to evaluate new therapeutic agents for the treatment of life threatening infections with Staphylococcus bacteria. A standard model, the Rabbit Infective Endocarditis Model, is used for these evaluations. Rabbits are provided appropriate anesthesia for surgical placement of catheters but are not given analgesic drugs following infection with bacteria.

   Rabbits undergo general surgical anesthesia by administration of the anesthetic combination of Ketamine/Xylazine and Butorphanol along with infiltration of the incision site with the Lidocaine. A carotid artery-to-left ventricle catheterization is performed. Subsequently, *Staphylococcus aureus* mediated infectious endocarditis is induced by intravascular injection of these bacteria.

   Treatment groups receive the test treatment compound or control vehicle approximately one day following bacterial challenge. Bacterial challenge occurs approximately 72 to 96 hours following catheterization.

   Study length is then approximately three to four days post-bacterial challenge. Following bacterial challenge the animals are observed for evidence of illness a minimum of twice daily. Some animals develop extensive infection. Infected animals most often have reduced food and water consumption and severely decreased activity. Animals exhibiting such behavior are immediately euthanized. Treatment efficacy is determined by the bacterial burden per gram of tissue. Early termination of animals with extensive infection is imperative for the analysis of the treatments.

5. **Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results:**

   The infectious disease model described in section 4 relies on a normally functioning immune system to evaluate the effectiveness of potential therapeutic antibodies engineered to promote bacterial clearance. Once the bacterial challenge is initiated, no further analgesics are administered due to their potential to alter the normal anti-microbial immune response. Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDS) were developed to suppress the inflammatory response through the

inhibition of cyclooxygenase. However, NSAIDS have also been shown to have effects on cytokine production[1], lymphocyte response[2] and neutrophil function[3]. Alternatively, opiate derived analgesics could be used, however, there is clear evidence that opiate derived analgesics have immunomodulatory effects both in animal models and in humans[4]. For these reasons, it is established practice to avoid the use of analgesics in *in vivo* models of immune function[5]. The use of post-operative analgesics in this model would interfere with our ability to interpret experimental results when using immune based therapies.

[1] Ertel, W., M. H. Morrison, D. R. Meldrum, A. Ayala and I. H Chaudry. 1992. Ibuprofen restores cellular immunity and decreases susceptibility to sepsis following hemorrhage. J. Surg. Res. 53(1): 55-61.

[2] Rossi Paccani, S., M. Boncristiano and C. T. Baldari. 2003. Molecular Mechanisms underlying suppression of lymphocyte responses by nonsteroidal anti-inflammatory drugs. Cell Mol. Life Sci. 60(6):1071-1083.

[3] Kang, K., S. J. Bae, W. M. Kim, D. H. Lee, U. Cho, M. H. Lee, M. S. Lee, S. Nam, K. E. Kuettner and D. E. Schwartz. 2000. Molecular characteristics of the inhibition of human neutrophil elastase by nonsteroidal anti-inflammatory drugs.

[4] Bryant, H. U. & J. W. Holoday. 1993. in *Opioids in Immunologic Processes*, ed. A Herz (Springer Berlin) Vol. 104/II, pp. 361-335.

[5] Piersma, F. E., M. A. Daemen, A. E. Bogaard, W. A. Buurman. 1999. Interference of pain control employing opioids in *in vivo* immunological experiments. Lab Anim. 33(4):328-333.

6. **What, if any federal regulations require this procedure?** No federal regulations require this procedure.